

SOLID-SELF EMULSIFYING DRUG DELIVERY SYSTEM: FORMULATION TECHNIQUES AND DOSAGE FORMS

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Received on : 16.03.2011

Revised : 21.05.2011

Accepted : 24.05.2011

ABSTRACT

The drug substance administered by any route must possess some aqueous solubility for systemic absorption. For this purpose, solubility is one of the most important parameter to achieve desired concentration of drug in systemic circulation for therapeutic response. However, more than 40% of new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery system, because of their low bioavailability. Self-emulsifying drug delivery systems (SEDDS) are usually used to improve the bioavailability of hydrophobic drugs. Conventional SEDDS, however, are mostly prepared in a liquid form, which can produce some disadvantages. Accordingly, solid SEDDS (S-SEDDS), prepared by solidification of liquid/semisolid self emulsifying (SE) ingredients into powders, have gained popularity. This article gives an overview of the recent advances in the study of S-SEDDS, especially the related solidification techniques and the development of solid SE dosage forms. Finally, the existing problems and the possible future research directions in this field are pointed out.

Keywords: *Solid-Self Emulsifying System; Solidification Techniques; self emulsifying; Recent Advances and Future aspects*

INTRODUCTION

As a consequence of modern drug discovery techniques, there has been a steady increase in the number of new pharmacologically active lipophilic compounds that are poorly water-soluble. It is a great challenge for pharmaceutical scientists to convert those molecules into orally administered formulations with sufficient bioavailability. One of the most popular and commercially viable formulation approaches for solving this problem is self-emulsifying drug delivery systems (SEDDS). SEDDS have been shown to be reasonably successful in improving the oral bioavailability of poorly water-soluble and lipophilic drugs¹⁻³. Traditional preparation of SEDDS involves dissolution of drugs in oils and blending with suitable solubilizing agents. However, SE formulations are normally prepared as liquids which possesses some disadvantages, for example, high production costs, low stability and portability, low drug loading and few choices of dosage forms. Irreversible drugs/excipients precipitation may also be problematic⁴. More importantly, the large quantity (30–60%) of surfactants in the formulations can induce gastrointestinal (GI) irritation. To address these problems, S-SEDDS have been investigated, as an alternative approach. Such systems require the solidification of liquid self-emulsifying (SE) ingredients into powders/nanoparticles to create various solid dosage forms (SE tablets^{5,6} and SE pellets^{7,8}, and so on). Thus, S-SEDDS combine the advantages of

SEDDS (i.e. enhanced solubility and bioavailability) with those of solid dosage forms (e.g. low production cost, convenience of process control, high stability and reproducibility, better patient compliance.). To date, there have been some studies that mainly focus on the preparation and characterization of a single, solid SE dosage form, yet relatively few that introduce S-SEDDS in a systemic way, especially with respect to dosage form development and preparation techniques.

Self-emulsifying drug delivery systems

SEDDS belong to lipid-based formulations. Lipid formulations can be oils, surfactant dispersions, emulsions, solid lipid nanoparticles, liposomes and SEDDS. SEDDS are isotropic mixtures of drug, oil/lipid, surfactant, and/or cosurfactant, which form fine emulsion/lipid droplets, ranging in size from approximately 100 nm (SEDDS) to less than 50 nm for self-microemulsifying drug delivery systems (SMEDDS), on dilution with physiological fluid. The drug, therefore, remains in solution in the gut, avoiding the dissolution step that frequently limits the absorption rate of hydrophobic drugs from the crystalline state⁹.

Excipients selection

The oily/lipid component is generally a fatty acid ester or a medium/long chain saturated, partially unsaturated or unsaturated hydrocarbon, in liquid, semisolid or solid form at room temperature. Examples include mineral oil, vegetable oil, silicon oil, lanolin, refined animal oil,

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fatty acids, fatty alcohols, and mono-/di-/tri-glycerides¹⁰. The most widely recommended surfactants are non-ionic surfactants with a relatively high hydrophilic-lipophilic balance (HLB) value. The surfactant concentration ranges between 30% and 60% (w/w) in order to form stable SEDDS³. More detailed descriptions are given elsewhere^{3, 11}, which can serve as a useful guide for excipients selection.

Biopharmaceutical issues

It is important to note that lipids (e.g. triglycerides) affect the oral bioavailability of drugs by changing biopharmaceutical properties, such as increasing dissolution rate and solubility in the intestinal fluid, protecting the drug from chemical as well as enzymatic degradation in the oil droplets and the formation of lipoproteins promoting lymphatic transport of highly lipophilic drugs¹². The absorption profile and the blood/lymph distribution of the drug depend on the chain length of the triglyceride, saturation degree, and volume of the lipid administered. Drugs processed by the intestinal lymph are generally transported to the systemic circulation in association with the lipid core of lipoproteins. In addition to the stimulation of lymphatic transport, administration of lipophilic drugs with lipids may enhance drug absorption into the portal blood compared with non-lipid formulations¹³.

Specificity

Self-emulsification depends on the nature of the oil/surfactant pair, surfactant concentration and oil/surfactant ratio, and the temperature at which self-emulsification occurs. Only very specific pharmaceutical excipients combinations lead to efficient self-emulsifying systems (SES). The efficiency of drug incorporation into a SEDDS is dependent upon the particular physicochemical compatibility of the drug/system^{3, 11}. So, pre-formulation solubility and phase diagram studies are required in order to obtain an optimal formulation design.

Characterization

The very essence of SEDDS is self-emulsification, which is primarily assessed visually. The efficiency of self-emulsification can be estimated by determining the rate of emulsification and droplet size distribution. The charge on the oil droplets of SEDDS is another property that needs to be assessed³. Melting properties and polymorphism of lipid or drug in SES may be established by X ray diffraction and differential scanning calorimetry.

METHODS OF PREPARATION

Solid self-emulsifying drug delivery system

SEDDS can exist in either liquid or solid states. SEDDS are usually, however, limited to liquid dosage forms, because many excipients used in SEDDS are not solids at room temperature. Given the advantages of solid

dosage forms, S-SEDDS have been extensively exploited in recent years, as they frequently represent more effective alternatives to conventional liquid SEDDS. From the perspective of dosage forms, S-SEDDS mean solid dosage forms with self-emulsification properties. S-SEDDS focus on the incorporation of liquid/semisolid SE ingredients into powders/nanoparticles by different solidification techniques e.g. adsorptions to solid carriers, spray drying, melt extrusion and nanoparticles technology. Such powders/nanoparticles, which refer to SE nanoparticles¹⁴/dry emulsions/solid dispersions, are usually further processed into other solid SE dosage forms or alternatively, filled into capsules (i.e. SE capsules). SE capsules also include those capsules into which liquid/semisolid SEDDS are directly filled without any solidifying excipients. To some extent, S-SEDDS are combinations of SEDDS and solid dosage forms, so many properties of S-SEDDS (e.g. excipients selection, specificity and characterization) are the sum of the corresponding properties of both SEDDS and solid dosage forms. For instance, the characterizations of SE pellets contain not only the assessment of self-emulsification, but also friability, surface roughness, and so on. In the 1990s, S-SEDDS were usually in the form of SE capsules, SE solid dispersions and dry emulsions, but other solid SE dosage forms have emerged in recent years, such as SE pellets/tablets, SE microspheres/nanoparticles and SE suppositories/implants.

FORMULATION TECHNIQUES OF S-SEDDS

Transforming liquid/semisolid SEDDS to S-SEDDS

Capsule filling with liquid and semisolid self-emulsifying formulations is the simplest and the most common technology for the encapsulation of liquid or semisolid SE formulations for the oral route. For semisolid formulations, it is a four-step process: (i) heating of the semisolid excipient to at least 20°C above its melting point; (ii) incorporation of the active substances (with stirring); (iii) capsule filling with the molten mixture and (iv) cooling to room temperature. For liquid formulations, it involves a two-step process: filling of the formulation into the capsules followed by sealing of the body and cap of the capsule, either by banding or by micro spray sealing¹⁵. In parallel with the advances in capsule technology proceeding, liquid-oro technology (Alza Corporation) has been designed for controlled delivery of insoluble drug substances or peptides. This system is based on osmotic principles and is a liquid SE formulation system. It consists of an osmotic layer, which expands after coming into contact with water and pumps the drug formulation through an orifice in the hard or soft capsule^{16, 17}. A primary consideration in capsule filling is the compatibility of the excipients with the capsule shell. The liquid/semisolid lipophilic vehicles compatible with hard capsules were listed by Cole, et al.¹⁸. The advantages

of capsule filling are simplicity of manufacturing; suitability for low-dose highly potent drugs and high drug loading (up to 50% (w/w)) potential.

Spray dried

Essentially, this technique involves the preparation of a formulation by mixing lipids, surfactants, drug, solid carriers, and solubilization of the mixture before spray drying. The solubilized liquid formulation is then atomized into a spray of droplets. The droplets are introduced into a drying chamber, where the volatile phase (e.g. the water contained in an emulsion) evaporates, forming dry particles under controlled temperature and airflow conditions. Such particles can be further prepared into tablets or capsules. The atomizer, temperature, suitable airflow pattern and drying chamber design are selected according to the drying characteristics of the product and powder specification.

Adsorption to solid carrier systems

Free flowing powders may be obtained from liquid SE formulations by adsorption to solid carriers. The adsorption process is simple and just involves addition of the liquid formulation onto carriers by mixing in a blender. The resulting powder may then be filled directly into capsules or alternatively, mixed with suitable excipients before compression into tablets. A significant benefit of the adsorption technique is good content uniformity. SEDDS can be adsorbed at high levels (up to 70% w/w) onto suitable carriers¹⁹. Solid carriers can be micro porous inorganic substances, high surface-area colloidal inorganic adsorbent substances, cross-linked polymers or nanoparticle adsorbents, for example, silica, silicates, magnesium trisilicate, magnesium hydroxide, talcum, croscopolvidone, cross-linked sodium carboxymethyl cellulose and cross linked polymethyl methacrylate²⁰. Cross-linked polymers create a favorable environment to sustain drug dissolution and also assist in slowing down drug reprecipitation²¹. Nanoparticle adsorbents comprise porous silicon dioxide (Sylysia 550), carbon nanotubes, carbon nanohorns, fullerene, charcoal and bamboo charcoal²².

Melt granulation

Melt granulation is a process in which powder agglomeration is obtained through the addition of a binder that melts or softens at relatively low temperatures. As a 'one-step' operation, melt granulation offers several advantages compared with conventional wet granulation, since the liquid addition and the subsequent drying phase are omitted. Moreover, it is also a good alternative to the use of solvent. The main parameters that control the granulation process are impeller speed, mixing time, binder particle size, and the viscosity of the binder. A wide range of solid and semisolid lipids can be applied

as meltable binders. Thereinto, Gelucire, a family of vehicles derived from the mixtures of mono-/di-/tri-glycerides and polyethylene glycols (PEG) esters of fatty acids, is able to further increase the dissolution rate compared with PEG usually used before, probably owing to its SE property²³. Other lipid-based excipients evaluated for melt granulation to create solid SES include lecithin, partial glycerides, or polysorbates. The melt granulation process was usually used for adsorbing SES (lipids, surfactants, and drugs) onto solid neutral carriers (mainly silica and magnesium aluminometa silicate)^{24, 25}.

Melt extrusion/extrusion spheronization

Melt extrusion is a solvent-free process that allows high drug loading (60%)¹⁵, as well as content uniformity. Extrusion is a procedure of converting a raw material with plastic properties into a product of uniform shape and density, by forcing it through a die under controlled temperature, product flow, and pressure conditions²⁶. The size of the extruder aperture will determine the approximate size of the resulting spheroids. The extrusion-spheronization process is commonly used in the pharmaceutical industry to make uniformly sized spheroids (pellets). The extrusion-spheronization process requires the following steps: dry mixing of the active ingredients and excipients to achieve a homogeneous powder; wet massing with binder; extrusion into a spaghetti-like extrudate; spheronization from the extrudate to spheroids of uniform size; drying; sifting to achieve the desired size distribution and coating (optional). In the wet masses comprising SES (Polysorbate 80 and mono-/di-glycerides), lactose, water and MCC, the relative quantities of SES and water had a significant effect on the extrusion force, size spread, disintegration time, and surface roughness of pellets. Studies suggested that the maximum quantity of this SES that can be solidified by extrusion spheronization occupies 42% of the dry pellet weight²⁷. Generally, the higher the water level, the longer the disintegration time²⁸. The rheological properties of wet masses may be measured by an extrusion capillary. It has been shown that SES containing wet mass with a wide range of rheological characteristics can be processed, but a single rheological parameter cannot be used to provide complete characterization by extrusion-spheronization²⁹. Applying extrusion-spheronization, SE pellets of diazepam and progesterone and bi-layered cohesive SE pellets have been prepared^{7, 30, 31}.

Dry emulsions

Dry emulsions are powders from which emulsion spontaneously occurs *in vivo* or when exposed to an aqueous solution. Dry emulsions can be useful for further preparation of tablets and capsules. Dry emulsion formulations are typically prepared from oil/water (O/W) emulsions containing a solid carrier

(lactose, maltodextrin, and so on) in the aqueous phase by rotary evaporation³², freeze-drying³³ or spray drying^{34–36}. Myers and Shively obtained solid state glass emulsions in the form of dry 'foam' by rotary evaporation, with heavy mineral oil and sucrose. Such emulsifiable glasses have the advantage of not requiring surfactant³². In freeze-drying, a slow cooling rate and the addition of amorphous cryoprotectants have the best stabilizing effects, while heat treatment before thawing decreases the stabilizing effects³³. The technique of spray drying is more frequently used in preparation of dry emulsions. The O/W emulsion was formulated and then spray-dried to remove the aqueous phase. The most exciting finding in this field ought to be the newly developed enteric-coated dry emulsion formulation, which is potentially applicable for the oral delivery of peptide and protein drugs. This formulation consisted of a surfactant, a vegetable oil, and a pH-responsive polymer, with lyophilization used³⁷. Recently, Cui et al. prepared dry emulsions by spreading liquid O/W emulsions on a flat glass, then dried and triturated to powders³⁸.

Self-emulsifying capsules

After the administration of capsules containing conventional liquid SE formulations, microemulsion droplet forms and subsequently disperses in the GI tract to reach sites of absorption. However, if irreversible phase separation of the microemulsion occurs, an improvement of drug absorption cannot be expected. For handling this problem, sodium dodecyl sulfate was added into the SE formulation³⁹. With the similar purpose, the supersaturable SEDDS was designed, using a small quantity of HPMC (or other polymers) in the formulation to prevent precipitation of the drug by generating and maintaining a supersaturated state *in vivo*. This system contains a reduced amount of a surfactant, thereby minimizing GI side effects^{40, 41}. Besides liquid filling, liquid SE ingredients also can be filled into capsules in a solid or semisolid state obtained by adding solid carriers (adsorbents, polymers, and so on). As an example, a solid PEG matrix can be chosen. The presence of solid PEG neither interfered with the solubility of the drug, nor did it interfere with the process of self-micro emulsification upon mixing with water^{42, 43}. Oral administration of SE capsules has been found to enhance patient compliance compared with the previously used parenteral route. For instance, low molecular weight heparin (LMWH) used for the treatment of venous thrombo-embolism was clinically available only via the parenteral route. So, oral LMWH therapy was investigated by formulating it in hard capsules. LMWH was dispersed in SMEDDS and thereafter the mixture was solidified to powders using three kinds of adsorbents: micro porous calcium silicate (Florite™ RE); magnesium aluminum silicate (Neusilin™ US2) and silicon dioxide (Sylsia™ 320). Eventually these solids were filled into hard capsules⁴⁴. In another study, such adsorbents were also applied

to prepare SE tablets of gentamicin that, in clinical use, was limited to administration as injectable or topical dosage forms¹⁹.

Self-emulsifying sustained/controlled-release tablets

Combinations of lipids and surfactants have presented great potential of preparing SE tablets that have been widely researched. Nazzal and Khan evaluated the effect of some processing parameters (colloidal silicates— X_1 , magnesium stearate mixing time— X_2 , and compression force— X_3) on hardness and coenzymum Q10 (CoQ10) dissolution from tablets of eutectic-based SMEDDS. The optimized conditions ($X_1 = 1.06\%$, $X_2 = 2$ min, $X_3 = 1670$ kg) were achieved by a face-centered cubic design⁴⁵. In order to reduce significantly the amount of solidifying excipients required for transformation of SEDDS into solid dosage forms, a gelled SEDDS has been developed by Patil et al. In their study, colloidal silicon dioxide (Aerosil 200) was selected as a gelling agent for the oil-based systems, which served the dual purpose of reducing the amount of required solidifying excipients and aiding in slowing down of the drug release⁴⁶. SE tablets are of great utility in obviating adverse effect, as disclosed by Schwarz in a patent. Inclusion of indomethacin (or other hydrophobic NSAID), for example, into SE tablets may increase its penetration efficacy through the GI mucosal membranes, potentially reducing GI bleeding. In these studies, the SES was composed of glycerol monolaurate and Tyloxapol™ (a copolymer of alkylphenol and formaldehyde). Polyethylene oxide successfully illustrated its suitability for controlled-release matrices. The resultant SE tablets consistently maintained a higher active ingredient concentration in blood plasma over the same time frame compared with a non-emulsifying tablet⁴⁷. The newest advance in the research field of SE tablet is the SE osmotic pump tablet, where the elementary osmotic pump system was chosen as the carrier of SES. This system has outstanding features such as stable plasma concentrations and controllable drug release rate, allowing a bioavailability of 156.78% relative to commercial carvedilol tablets⁴⁸.

Self-emulsifying sustained/controlled-release pellets

Pellets, as a multiple unit dosage form, possess many advantages over conventional solid dosage forms, such as flexibility of manufacture, reducing intrasubject and intersubject variability of plasma profiles and minimizing GI irritation without lowering drug bioavailability⁴⁹. Thus, it is very appealing to combine the advantages of pellets with those of SEDDS by SE pellets. Serratori et al. prepared SE controlled-release pellets by incorporating drugs into SES that enhanced their rate of release, and then by coating pellets with a water-insoluble polymer that reduced the rate of drug release. Pellets

were prepared by extrusion/spheronization contained two water-insoluble model drugs (methyl and propyl parabens) and by SES contained mono-diglycerides and Polysorbate 80^{50, 51}.

Self-emulsifying solid dispersions

Solid dispersions although could increase the dissolution rate and bioavailability of poorly water-soluble drugs, some manufacturing difficulties and stability problems existed. Serajuddin pointed out that these difficulties could be surmounted by the use of SE excipients^{52, 53}. These excipients have the potential to increase further the absorption of poorly water-soluble drugs relative to previously used PEG solid dispersions and may also be filled directly into hard gelatin capsules in the molten state, thus obviating the former requirement for milling and blending before filling^{9,54}. SE excipients like Gelucire 144/14, Gelucire 150/02, Labrasco I1, Transcuto I1 and TPGS (tocopheryl polyethylene glycol 1000 succinate) have been widely used in this field^{52–55}. For example, Gupta et al. prepared SE solid dispersion granules using the hot-melt granulation method. Seven drugs, including four carboxylic acid containing drugs, a hydroxyl-containing drug, an amide-containing drug (phenacetin) and a drug with no proton-donating groups (progesterone) were chosen. Gelucire 150/13 was used as the dispersion carrier, whereas Neusilin US2 was used as the surface adsorbent²⁵.

Self-emulsifying beads

Transformation of SES into a solid form with minimum amounts of solidifying excipients, Patil and Paradkar investigated loading SES into the microchannels of porous polystyrene beads (PPB) using the solvent evaporation method. PPB with complex internal void structures is typically produced by copolymerizing styrene and divinyl benzene. They are inert, stable over a wide pH range and to extreme conditions of temperature and humidity. This research concluded that PPB was potential carriers for solidification of SES, with sufficiently high SES to PPB ratios required to obtain solid form. Geometrical features, such as bead size and pore architecture of PPB, were found to govern the loading efficiency and in vitro drug release from SES-loaded PPB⁵⁶.

Self-emulsifying sustained-release microspheres

Zedoary turmeric oil (ZTO; a traditional Chinese medicine) exhibits potent pharmacological actions including tumor suppressive, antibacterial, and antithrombotic activity. With ZTO as the oil phase, You et al. prepared solid SE sustained-release microspheres using the quasi-emulsion–solvent-diffusion method of the spherical crystallization technique. ZTO release behavior could be controlled by the ratio of hydroxypropyl methylcellulose acetate succinate to Aerosil 200 in the formulation. The plasma

concentration–time profiles were achieved after oral administration of such microspheres to rabbits, with a bioavailability of 135.6% with respect to the conventional liquid SEDDS⁵⁷.

Self-emulsifying nanoparticles

Nanoparticle techniques have been useful in the production of SE nanoparticles. Solvent injection is one of these techniques. In this method, the lipid, surfactant, and drugs were melted together, and injected drop wise into a stirred non-solvent. The resulting SE nanoparticles were thereafter filtered out and dried. This approach yielded nanoparticles (about 100 nm) with a high drug loading efficiency of 74%⁵⁸. A second technique is that of sonication emulsion–diffusion–evaporation, by which is co-loading 5-fluorouracil (5-FU) and antisense EGFR (epidermal growth factor receptor) plasmids in biodegradable PLGA/O-CMC nanoparticles were realized. The mixture of PLGA (poly-lactide-co-glycolide) and O-CMC (O-carboxymethyl-chitosan) had a SE effect, with no need to add another surfactant stabilizer. Eventually the 5-FU and plasmid encapsulation efficiencies were as high as 94.5% and 95.7%, respectively, and the 5-FU release activity from such nanoparticles could be sustained for as long as three weeks⁵⁹. More recently, Trickler et al. developed a novel nanoparticles drug delivery system consisting of chitosan and glyceryl mono oleate (GMO) for the delivery of paclitaxel (PTX). These chitosan/GMO nanoparticles with bioadhesive properties and increased cellular association were prepared by multiple emulsion (o/w/o) solvent evaporation methods. The SE property of GMO enhanced the solubility of PTX and provided a foundation for chitosan aggregation, meanwhile causing near 100% loading and entrapment efficiencies of PTX. These advantages allow the use of lower doses of PTX to achieve an efficacious therapeutic window, thus minimizing the adverse side effects associated with chemotherapeutics like PTX⁶⁰.

Self-emulsifying suppositories

Some investigators proved that S-SEDDS could increase not only GI adsorption but also rectal/vaginal adsorption⁶¹. Glycyrrhizin, which, by the oral route, barely achieves therapeutic plasma concentrations, can obtain satisfactory therapeutic levels for chronic hepatic diseases by either vaginal or rectal SE suppositories. The formulation included glycyrrhizin and a mixture of a C6–C18 fatty acid glycerol ester and a C6–C18 fatty acid macrogol ester⁶².

Self-emulsifying implants

Research into SE implants has greatly enhanced the utility and application of S-SEDDS. As an example, 1,3-bis(2-chloroethyl)-1-nitrosourea (carmustine, BCNU) is a chemotherapeutic agent used to treat malignant brain tumors. However, its effectiveness was hindered

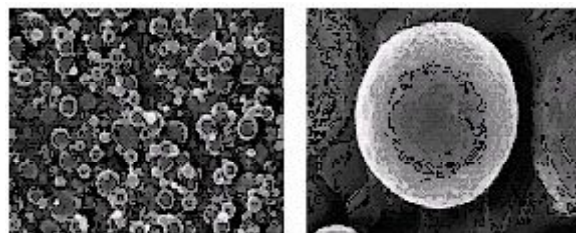
by its short half-life. In order to enhance its stability compared with that released from poly (D,L-lactide-co-glycolide) (PLGA) wafer implants, SES was formulated with tributyrin, Cremophor RH 40 (polyoxyl 40 hydrogenated castor oil) and Labrafil 1944 (polyglycolized glyceride). Then the self-emulsified BCNU was fabricated into wafers with flat and smooth surface by compression molding. Ultimately, SES increased *in vitro* half-life of BCNU upto 130 min contrasted with 45 min of intact BCNU. *In vitro* release of BCNU from SE PLGA wafers were prolonged upto 7 days. Such wafers had higher *in vitro* antitumor activity and were less susceptible to hydrolysis than those wafers devoid of SES⁶³. Loomis invented copolymers having a bioresorbable region, a hydrophilic region and at least two cross-linkable functional groups per polymer chain. Such copolymers show SE property without the requirement of an emulsifying agent. These copolymers can be used as good sealants for implantable prostheses⁶⁴.

CONCLUSION

SEDDS are a promising approach for the formulation of drugs with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SEDDS, which have been shown to substantially improve oral bioavailability. As mentioned above, numerous studies have confirmed that SEDDS substantially improved solubility/dissolution, absorption and bioavailability of poorly water-soluble drugs. As improvements or alternatives of conventional liquid SEDDS, S-SEDDS are superior in reducing production cost, simplifying industrial manufacture, and improving stability as well as patient compliance. Most importantly, S-SEDDS are very flexible to develop various solid dosage forms for oral and parenteral administration. Moreover, GI irritation is avoidable and controlled/sustained release of drug is achievable. There is still a long way to go, however, before more solid SE dosage forms (except for SE capsules) appear on the market. Because there exist some fields of S-SEDDS to be further exploited, such as studies about human bioavailability and *in vitro/in vivo* correlation. Moreover, the researches of S-SEDDS lose their balance, that is, SE implants/suppositories/microspheres have not been as extensively studied as SE tablets/pellets/capsules. It is also worth pointing out some issues to which much attention should be paid, for example physical aging phenomenon associated with glyceride, oxidation of vegetable oil⁶⁵, and interaction between drugs and excipients⁶⁶. Selection of suitable excipients is the main hurdle of developing S-SEDDS⁵³. Thus, these aspects should represent the major future working directions for S-SEDDS.

ACKNOWLEDGEMENTS

I am grateful to Bo Tang, Dr. S.L. Carney for their art work to enhance this manuscript greatly and in a successful way.



Scanning Electron Microscopy (SEM) images of the solid SEDDS

List of abbreviations

SEDDS	: Self-Emulsifying Drug Delivery System
GI	: Gastrointestinal
S-SEDDS	: Solid- Self Emulsifying Drug Delivery System
HLB	: Hydrophilic-Lipophilic Balance
SES	: Self-Emulsifying System
SEM	: Scanning Electron Microscopy
PEG	: Polyethylene glycol
LMWH	: Low molecular weight heparin
NSAID	: Non Steroid Anti Inflammatory Drug
TPGS	: Tocopheryl Polyethylene glycol
PPB	: Porous polystyrene beads
ZTO	: Zedoary turmeric oil
EGFR	: Epidermal growth factor receptor
PLGA	: Poly-lactide-co-glycolide
O-CMC	: O-carboxymethyl-chitosan
FU	: Fluorouracil
GMO	: Glyceryl monooleate
PTX	: Paclitaxel
BCNU	: Bis-Chloroethyl Nitrosourea Carmustine,

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